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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 22

Application Number: 09/687,051
Filing Date: October 12, 2000
Appellant(s): BUECHLER et al.

Barry Wilson
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed August 20, 2003.

1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 69, 70, 79-83, 86-89, 91, and 92 stand or fall together and claims 84, 85, 90, and 93 stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

No prior art is relied upon by the examiner in the rejection of the claims under appeal.

(10) Grounds of Rejection

The following grounds of rejection are applicable to the appealed claims:

Claims 69, 70, 79-83, 86-89, 91, and 92 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for a cocktail of insensitive antibodies, wherein each antibody binds each one of the free cTnI, binary complex of cTnI, and ternary complex of cTnI for use in an assay for determining free and complexed cardiac specific isoforms of troponin (cTnI), does not reasonably provide enablement for a single insensitive antibody, which binds each one and all of free cTnI, binary complex of cTnI, and ternary complex of cTnI for use in an assay for determining free and complexed cTnI. The specification does not enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection is set forth in prior Office Action, Paper No. 15.

As set forth in In re Wands, 858 F .2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining, whether a disclosure would require undue experimentation include 1) the nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of those in the art, and 8) the breadth of the claims.

The nature of the invention- the invention is directed to insensitive antibodies which bind each one of the free, binary complex, and ternary complex isoforms of cTnI for use in a method for determining the presence or amount of each and all of free, binary and ternary complexed isoforms of cTnI.

The state of the prior art- ***the prior art of record fails to disclose an insensitive antibody which binds each and all of the free, binary, and ternary complexed isoforms of cTnI for use in a method for determining the presence or amount of all free, binary and ternary complexed isoforms of cTnI.***

The predictability or lack thereof in the art- ***there is no predictability based on the instant specification that a single insensitive antibody binds each and all of the free, binary, and ternary complexed isoforms of cTnI for use in a method of determining the presence or amount of all of the free, binary and ternary complexed isoforms of cTnI in a sample.***

The amount of direction or guidance present- appropriate guidance is provided by the specification for a cocktail of insensitive antibodies that have been generated to specifically bind each one of the free, binary, and ternary complexed isoforms of cTnI for use in a method to determine the presence or amount of all of the free, binary and ternary complexed isoforms of cTnI in a sample. However, the specification fails to provide guidance to provide a single insensitive antibody that specifically binds all of the free, binary and ternary complexed isoforms of cTnI to determine the total concentration of a cTnI isoform the claimed in an assay.

The presence or absence of working examples- working examples are provided in the specification that show a cocktail of insensitive antibodies that bind each one of the free, binary, and ternary complexed isoforms of cTnI for use in determining all of the free, binary and ternary complexed isoforms of cTnI in a sample. There are no working examples that show analogous results using a single insensitive antibody, which is encompassed by the broad scope of the instant claims.

The quantity of experimentation necessary- it would require undue amount of experimentation for the skilled artisan to make and use the method as claimed.

The relative skill of those in the art-the level of skill in the art is high.

The breadth of the claims- as recited, the instant claims are directed to a single insensitive antibody that binds all of the free, binary and ternary complexed isoforms of cTnI for use in a method of determining the presence or amount of all free, binary, and ternary complexed isoforms of cTnI in a sample. As recited, the instant single insensitive antibody has specific binding for each of the free, binary, and ternary complexed isoforms of cTnI and is capable of determining the presence or amount of each and all of free, binary, and ternary complexed isoforms of cTnI in as sample.

In this case, the specification at pages 6-7 describes antibodies for use in a method that are monoclonal, polyclonal, fragment thereof, and recombinant . These antibodies are characterized as being "sensitive" or "insensitive", the sensitive antibodies tend to bind and exhibit preferential detection of a single form of troponin and the insensitive antibodies tend to bind and exhibit detection of more than one form of troponin, i.e. free, binary, or complexed form, but having only one conserved epitope

common to all for binding the antibody. In pages 13-14, the specification shows that an insensitive antibody is utilized to bind to the free and complexed forms of troponin; that is, insensitive with respect to the oxidized, reduced, and complexed forms of troponin. Alternatively, more than one sensitive antibody would be necessary to measure both the free and complexed forms of troponin. At pages 21-22, the specification shows how to generate and select antibodies that are sensitive or insensitive to the binding of free troponin I or T, troponin I or T in binary complexes, and troponin I or T in ternary I/T/C complexes; this is accomplished by purification of free troponin I or T, binary troponin I/T, T/C, and I/C complexes and ternary I/T/C complexes, respectively, then injection into mice or rabbits to generate monoclonal or polyclonal antibodies. The antibodies are then screened for affinity and specificity with the purified free troponin, binary complexes of troponin, and ternary complexes of troponin.

While the specification at pages 29-31 exemplifies selected antibodies, i.e. a cocktail of antibodies, that bind one of the free cTnI, binary complexed cTnI, and ternary complexed cTnI, for use in a method of determining the amount of free, binary complexed, and ternary complexed cTnI, the specification does not show any working examples of a single insensitive antibody that has binding for all of the free cTnI, binary complexed cTnI, and ternary complexed cTnI. The fact that insensitive antibodies that bind more than one form of cTnI has been characterized, is not sufficient to enable the breadth of the claimed method to use a single insensitive antibody in an assay to determine the presence or amount of all of free cTnI, binary complexed cTnI, and ternary complexed cTnI. The specification does not establish a direct correlation

between using a cocktail of insensitive and/or sensitive antibodies and a single "insensitive" antibody, which would lead the skilled artisan to say that the claimed method works for a single insensitive antibody to enable the breadth of the claimed method. The specification does not provide any teaching that suggests that an antibody generated against purified free cTnI, an antibody generated against purified binary complexed cTnI, or an antibody generated against purified ternary complexed cTnI, can be characterized to bind a conserved epitope for each and all of said free cTnI, binary complexed cTnI, and ternary complexed cTnI in a sample. Further, the working examples at Example 15 and Example 16, also utilize a cocktail of insensitive antibodies to determine the presence or amount of all of free cTnI, binary complexed cTnI, and ternary complexed cTnI in a sample. While it is not necessary to show working examples for every possible embodiment, there should be sufficient teachings in the specification that would suggest to the skilled artisan that the breadth of the claimed method is enabled. This is not the case in the instant specification. Thus, the claimed method is only enabled for a cocktail of insensitive antibodies which bind each one of the free cTnI, binary complexed cTnI, and ternary complexed cTnI for use in a method of determining the presence of all of free cTnI, binary complexed cTnI, and ternary complexed cTnI in a sample.

In view of the teachings of In re Wands, 8 USPQ2d 1400, it has been determined that the level of experimentation required to enable the breadth of the claims is undue. It has been set forth above that 1) the experimentation required to enable a single insensitive antibody to determine the presence of all of free cTnI, binary complexed

cTnI, and ternary complexed cTnI in a sample, would be great as 2) there is no experimental evidence provided that would indicate that the claimed method would work using a single insensitive antibody; 3) there is no proper guidance that shows that a single insensitive antibody has been generated, characterized, and selected to bind each and all of free cTnI, binary complexed cTnI, and ternary complexed cTnI, 4) the nature of the invention is a cocktail of antibodies which bind each one of the free cTnI, binary complexed cTnI, and ternary complexed cTnI for use in a method of determining the presence of all of free cTnI, binary complexed cTnI, and ternary complexed cTnI in a sample, 5) the relative skill of those in the art is high, yet 6) the state of the prior art has been shown to be unpredictable as evidenced by the fact that no prior art has been cited that shows generation, characterization, and selection of an antibody that has specific binding for each and all of free cTnI, binary complexed cTnI, and ternary complexed cTnI, and lastly 7) the claims broadly recite a single insensitive antibody which binds each one of free cTnI, binary complexed cTnI, and ternary complexed cTnI for use in a method of determining the presence of all of free cTnI, binary complexed cTnI, and ternary complexed cTnI in a sample, without specifically stating how this can be done without undue experimentation.

Therefore, it is maintained that one of ordinary skill in the art could not make and use the invention as claimed without undue experimentation.

(11) Response to Argument

4. Applicant's arguments filed 8/20/03 have been fully considered but they are not persuasive.

A) Appellant contends that use of the term "antibody" is enabled because the term "antibody" encompasses both monoclonal antibodies and polyclonal antibodies. According to Appellant, polyclonal antibody is by definition, a mixture of different monoclonal antibodies. Appellant, therefore, argues that the specification is enabled since Examiner has indicated that the instant specification is enabled with respect to a pool of antibodies, which requires that a polyclonal antibody of the claims would similarly be enabled.

In response, the claims recite "An antibody", "A composition comprising: one or more antibodies", and "A method ... comprising: selecting one or more antibodies" which all encompass both "monoclonal antibody" and "polyclonal antibody". The recitation of "An antibody" or "one ... antibody" does not exclude monoclonal antibody.

Contrary to Appellant's argument, a polyclonal antibody is not a mixture of different monoclonal antibodies. A monoclonal antibody or monoclonal antibodies are antibody molecules having common specificity. A polyclonal antibody or polyclonal antibodies are antibody molecules having different specificities. The definition of polyclonal antibody is thus, contradictory to Appellant's claim to "an antibody that has *specific binding to* cTnI in free cTnI form, cTnI in binary from complexed with troponin C, and cTnI in ternary form complexed with troponin C and troponin T. Appellant claims that the "an antibody" has a requisite common specificity to the conserved epitope common to each and all of the free cTnI, cTnI in binary form complexed with troponin C,

and cTnI in ternary form complexed with troponin C and troponin T. Accordingly, for the specification to be enabled, it is required to provide a teaching that suggests an antibody to be *monoclonal* that is generated against purified free cTnI, an antibody that is generated against purified binary complexed cTnI, or an antibody that is generated against purified ternary complexed cTnI, and that has been fully and successfully characterized to bind one common specific *conserved epitope for each and all of the free cTnI, binary complexed cTnI, and ternary complexed cTnI*. All the working examples at Example 15 and Example 16, utilize a cocktail of insensitive antibodies to determine the presence or amount of each and all of free cTnI, binary complexed cTnI, and ternary complexed cTnI in a sample; thus, Appellant's instant specification is not enabled for the claimed invention.

B) Appellant submits that the Beuchler declaration is evidence that must be considered and that Examiner has failed to weigh the evidence as a whole, a consideration that is fundamental in any determination of enablement.

In response, the Beuchler declaration, having been substantially considered in previous responses, is an opinion declaration of Appellant as an interested party; thus, the Beuchler declaration is of reduced scientific probative value.

C) Appellant argues that Examiner has dismissed the declaration on the basis of an improper evidentiary standard, which requires actual data to prove enablement.

In response, both of Appellant's disclosure and declaration provide information that is prophetic in nature and state speculations in place of factual evidence to meet evidentiary standards to support the recited claims. Evidentiary standard, to be proper, requires that experimentation is undue by showing predictability and success, i.e. by generation or production of the "one antibody" having the requisite common specificity as recited in the rejected claims, in addition to direction or guidance presented in making such antibody. Presence of working examples, also show success and/or that only reasonable quantity of experimentation is necessary, to enable a disclosure. Neither the disclosure nor the declaration fail to meet evidentiary standards as set for in In re Wands.

D) Appellant argues that Examiner's reply to Appellant's arguments with regards to "insensitive antibody" as being "one that will tend to bind to more than one form of troponin, i.e. each one of free cTnI, cTnI in binary complex with troponin C, and cTnI in ternary complex with troponin C and troponin T, as recited in the claims" is contradictory to Examiner's position.

In response, Examiner's position is not contradictory to the statement that "an insensitive antibody is one that will tend to bind to more than one form of troponin, i.e. each one of free cTnI, cTnI in binary complex with troponin C, and cTnI in ternary complex with troponin C and troponin T, as recited in the claims" because the required binding of the antibody as recited in the claims is to only one conserved epitope common to all of the cTnI forms, i.e. free, binary, or complexed form.

E) Appellant argues that Examiner applied an improper legal standard for judging compliance with enablement requirement since the presence of working examples is one consideration but is not the single determinative consideration.

In response and as set forth in In re Wands, enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Undue experimentation requires predictability and success in addition to direction or guidance presented, both of which are absent in Appellant's disclosure. Presence of working examples, also show success and/or reasonable quantity of experimentation necessary, but is also lacking in Appellant's disclosure. To reiterate, the specification at pages 29-31 exemplifies selected antibodies, i.e. a cocktail of antibodies, that bind one of the free cTnI, binary complexed cTnI, and ternary complexed cTnI, for use in a method of determining the amount of free, binary complexed, and ternary complexed cTnI, the specification does not show any working examples of a single insensitive antibody that has binding for all of the free cTnI, binary complexed cTnI, and ternary complexed cTnI. However, the specification does not show any working examples of the claimed single antibody that would have been successfully generated that has specific binding for each and all of the free cTnI, binary complexed cTnI, and ternary complexed cTnI. The fact that insensitive antibodies that bind more than one form of cTnI has been characterized, is not sufficient to enable the breadth of the claimed method to use a single insensitive antibody in an assay to determine the presence or amount of all of free cTnI, binary complexed cTnI, and

ternary complexed cTnI. Additionally, the specification does not provide any teaching that suggests that an antibody generated against purified free cTnI, an antibody generated against purified binary complexed cTnI, or an antibody generated against purified ternary complexed cTnI, has been successfully characterized to bind a conserved epitope for each and all of said free cTnI, binary complexed cTnI, and ternary complexed cTnI in a sample. While it is not necessary to show working examples for every possible embodiment, there should be sufficient teachings in the specification that would suggest to the skilled artisan, a level of success and predictability, by showing generation or production of the one single antibody capable of binding as claimed, so as to enable the breadth of the claimed invention. This is not the case in the instant specification. Thus, the claims are only enabled for a cocktail of insensitive antibodies that bind each one of the free cTnI, binary complexed cTnI, and ternary complexed cTnI for use in a method of determining the presence of all of free cTnI, binary complexed cTnI, and ternary complexed cTnI in a sample.

F) Appellant argues that in addition to the substantial guidance provided in the specification, Appellant submitted a declaration of Dr. Beuchler as evidence of predictability, describing why the skilled artisan would reasonably believe that the claimed antibody *could* be obtained.

In response, page 21, line 3 to page 22, line 19 provides generation and selection of antibodies that are preferentially either sensitive or insensitive to the binding of troponin I or T in binary complexes. It further provides generation and selection of

antibodies that are preferentially either sensitive or insensitive to the binding of troponin I or T in ternary complexes. The antibodies are generated and selected by first screening for affinity and specificity with the purified binary or ternary complexes. However, nowhere in the specification specifically shows of any generation and selection of an insensitive antibody having a conserved epitope that binds each one and all of the free, binary, and ternary complexed form of cTnI, to encompass that the scope of the claimed invention.

Further, statements in Appellant's arguments such as "antigenic sites *may* remain available for antibody binding, ... and *may* be used bind a free cardiac troponin I ...", "antibodies ... would be *expected to bind* ..., would also be expected to be available", and "even a monoclonal antibody *could* be produced having the requisite specificity", as well as statements in the declaration specifically in paragraphs 3, 4, 5, and 6 such as "can be performed", "regions may be present", "may obscure one or more cardiac specific regions ... may remain accessible ... antibodies may thus be selected ...", provide speculations which fail to provide factual evidence for the record and only confirm the prophetic nature of the disclosure. To reiterate, enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Undue experimentation requires predictability and success, that it has been successfully made, i.e. submission of a hybridoma cell that produces the "an antibody" that has specific binding for the conserved epitope for each and all of said free cTn, binary complexed cTn, and ternary complexed cTn, in addition to direction or guidance presented, both of which are absent in Appellant's disclosure and declaration.

Presence of working examples using the "an antibody", also show success, i.e. that it has been successful, and that only reasonable quantity of experimentation is necessary, both of which are lacking in Appellant's disclosure and declaration.

G) Appellant argues that Examiner's interpretation of the meaning of "an antibody" as a single antibody, is without support of any evidence of record.

In response to Appellant's argument, which appears to intend excluding claiming to "a single antibody", it has been noted that use of the phrase "a single antibody" denotes a singular type or form of an element and does not *necessarily* imply a population, i.e. antibodies. This interpretation is analogous to Appellant's own claims which recite "selecting one *or more* antibodies ..." in claim 81 and "one *or more* antibodies" in claim 79. Thus, the phrase "or more" provides evidentiary confirmation in Appellant's disclosure that "an antibody" is intended as one or single antibody.

Claims 71-74 are allowable. Claims 84, 85, 90, and 93 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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November 25, 2003

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